

Amendments to the Specification:

Please replace the paragraph beginning at page 2, line 27 with the following amended paragraph:

**[0006]** Particularly, the latter method using poly(vinylpyrrolidone) has attracted keen interests in view of safety and cost, and the above-discussed problems can be solved by this method. However, the hydrophilicity-imparting technique by adding poly(vinylpyrrolidone) has a problem in that poly(vinylpyrrolidone) elutes from membranes and contaminates the purified blood during a hemodialysis. When the amount of eluting poly(vinylpyrrolidone) becomes larger, the amount of poly(vinylpyrrolidone), as foreign materials to the organisms, accumulated in vivo becomes larger over a long period of hemodialysis, which is likely to induce side effects or complications. To solve such disadvantages, the amount of eluting poly(vinylpyrrolidone) is regulated in the Approval Standard for Dialysis-type Artificial Kidney Apparatus, and is determined by UV absorbance according to these standards. In the meantime, a technique for evaluating the ~~eluation~~ elution amount-controlling effect based on these standards is disclosed (cf. Patent Literatures 5 to 7).

Please replace the paragraph beginning at page 6, line 31 with the following amended paragraph:

**[0013]** The present invention relates to a polysulfone permselective hollow fiber membrane bundle which contains poly(vinylpyrrolidone), and particularly to a polysulfone permselective hollow fiber membrane bundle which shows a hydrogen peroxide-eluting amount of 5 ppm or less therefrom, when subjected to an ~~eluation~~ elution test regulated in the Approval Standard for Dialysis-type Artificial Kidney Apparatus.

Please replace the paragraph beginning at page 7, line 8 with the following amended paragraph:

Also, the present invention pertains to a polysulfone permselective hollow fiber membrane bundle, which shows a hydrogen peroxide concentration of 5 ppm or less in every one of eluates from 10 portions into which the hollow fiber membrane bundle is divided in the

lengthwise direction, when each of such portions is subjected to an ~~eluation~~ elution test regulated in the Approval Standard for Dialysis-type Artificial Kidney Apparatus.

Please replace the paragraph beginning at page 7, line 16 with the following amended paragraph:

Further, the present invention relates to a polysulfone permselective hollow fiber membrane bundle, which shows a poly(vinylpyrrolidone)-eluting amount of 10 ppm or less therefrom, when subjected to an ~~eluation~~ elution test regulated in the Approval Standard for Dialysis-type Artificial Kidney Apparatus.

Please replace the paragraph beginning at page 12, line 1 with the following amended paragraph:

It is preferably recommended to replace the inner atmospheres of supply tanks, etc. with an inert gas in a raw material-supply system, in the course of the manufacturing of the hollow fiber membrane bundle. Poly(vinylpyrrolidone) which is reduced in hydrogen peroxide content by the recrystallization method or the ~~eluation~~ elution method may also be used.

Please replace the paragraph beginning at page 14, line 7 with the following amended paragraph:

The amount of poly(vinylpyrrolidone) eluting from the hollow fiber membrane bundle is determined by using an eluate which is obtained according to the ~~eluation~~ elution test method regulated in the Approval Standard for Dialysis-type Artificial Kidney Apparatus. In detail, some hollow fiber membranes (1.0 g) are optionally removed from a dried hollow fiber membrane bundle, and 100 ml of RO water is added to the hollow fiber membranes, followed by ~~eluation~~ elution therefrom at 70°C for one hour to obtain an eluate.

Please replace the paragraph beginning at page 18, line 1 with the following amended paragraph:

[0027] The amount of eluting hydrogen peroxide is also determined by using an eluate obtained by a method according to the ~~eluation~~ elution test method regulated in the Approval Standard for Dialysis-type Artificial Kidney Apparatus.

Please replace the paragraph beginning at page 18, line 6 with the following amended paragraph:

[0028] In the present invention, the polysulfone permselective hollow fiber membrane bundle is divided and cut along the lengthwise direction thereof, to obtain 10 portions thereof, each of which is then measured for the amount of hydrogen peroxide eluting therefrom. Preferably, all the portions show hydrogen peroxide-eluting amounts of 5 ppm or less. As described above, when hydrogen peroxide is present in a specified site of the hollow fiber membrane bundle, the deterioration reaction of the materials of the hollow fiber membrane bundle starts from such a site and transmits to a whole of the hollow fiber membrane bundle. Therefore, it is needed that the content of hydrogen peroxide in the hollow fiber membrane bundle for use as a module should be maintained at a given amount or less alongside the overall lengthwise direction thereof. The oxidation deterioration of poly(vinylpyrrolidone) initiated by hydrogen peroxide present in a specified site of the hollow fiber membrane bundle sequentially spreads all over the hollow fiber membrane bundle, so that the amount of hydrogen peroxide further increases due to such deterioration, and simultaneously, the molecular weight of the deteriorated poly(vinylpyrrolidone) decreases, which facilitates the ~~eluation~~ elution of such poly(vinylpyrrolidone) from the hollow fiber membrane bundle. Because of this sequential deterioration reaction, the amounts of eluting hydrogen peroxide and poly(vinylpyrrolidone) increase while the hollow fiber membrane bundle is being stored over a long period of time, which results in poor safety when the hollow fiber membrane bundle is used as a blood purifier.

Please replace the paragraph beginning at page 19, line 28 with the following amended paragraph:

[0030] When the hollow fiber membrane bundle of the present invention is subjected to an ~~eluation~~ elution test regulated in the Approval Standard for Dialysis-type Artificial Kidney Apparatus after having stored at a room temperature for one year, the maximum of the UV

absorbances of the eluate at a wavelength of 220 to 350 nm is preferably 0.10 or less, more preferably 0.08 or less. The hollow fiber membrane bundle can gain this feature, by decreasing, to 5 ppm or less, the amounts of hydrogen peroxide eluting from all the above 10 portions into which the hollow fiber membrane bundle has been divided along the lengthwise direction.

Please replace the paragraph beginning at page 21, line 11 with the following amended paragraph:

**[0033]** As another method to inhibit the ~~generaion~~ generation of hydrogen peroxide, it is also important to dissolve a membrane-forming solution in shorter time. To form the solution in shorter time, it is effective to raise the dissolving temperature and/or to increase the stirring rate. However, the deterioration and decomposition of poly(vinylpyrrolidone) tend to proceed because of the influences of the temperature, the stirring rate and the shearing force, when such measures are taken. In fact, as a result of the present inventors' researches, it is confirmed that the peak top of the molecular weight of poly(vinylpyrrolidone) in a membrane-forming solution shifts in the decomposing direction (i.e. on the side of lower molecular weights) along with an increase in the dissolving temperature, and that a shoulder which seems to indicate a decomposed product appears on the side of the lower molecular weights. Thus, raising the dissolving temperature in order to improve the dissolving rate of raw materials accelerates the deterioration/decomposition of poly(vinylpyrrolidone), which leads to the blending of a decomposed product of poly(vinylpyrrolidone) into the resultant permselective hollow fiber membrane. When such a hollow fiber membrane is used in, for example, a blood purifier, such a decomposed product elutes into the blood. Therefore, the quality and safety of such a blood purifier are inferior.

Please replace the paragraph beginning at page 38, line 20 with the following amended paragraph:

**[0055]** In the present invention, it is important to suppress the content of poly(vinylpyrrolidone) in the outer surface of the hollow fiber membrane within a specified range, in order to balance the actions of preventing the ~~eluation~~ elution of poly(vinylpyrrolidone) and the infiltration of endotoxin into the blood side and of preventing the sticking of the hollow fiber membranes to one another while they are being dried. To adjust the content of poly(vinylpyrrolidone) within

such a specified range, for example, the ratio of poly(vinylpyrrolidone) to a polysulfone polymer is adjusted within a specified range, and the conditions for manufacturing the hollow fiber membranes are optimized. It is also an effective method to wash the resultant hollow fiber membranes. The following are effectively employed as the membrane-forming conditions: that is, the humidity of the air gap of the exit of a nozzle is controlled; the drawing condition, the temperature of a coagulation bath, and the composition ratio of a solvent to a non-solvent in a coagulating liquid are optimized; and a washing step is included.

Please replace the paragraph beginning at page 43, line 14 with the following amended paragraph:

**[0060]** This blood purifier is stored at room temperature for one year, and then is subjected to an ~~eluation~~ elution test regulated in the Approval Standard for Dialysis-type Artificial Kidney Apparatus, so as to measure the UV absorbance of an eluate obtained therefrom. In one of the preferred embodiments of the present invention, the maximum of the UV absorbance of the eluate at a wavelength of from 220 to 350 nm is 0.10 or less, more preferably 0.08 or less.

Please replace the paragraph beginning at page 60, line 24 with the following amended paragraph:

**[0083]** A blood purifier was fabricated, using the obtained hollow fiber membrane bundle, so as to carry out a leak test. As a result, there was observed no failure in adhesion due to the sticking of the hollow fiber membranes to one another. The blood purifier was filled with RO water, and then was irradiated with  $\gamma$ -rays at an absorbed dose of 25 kGy for a crosslinking treatment. After the irradiation with  $\gamma$ -rays, the hollow fiber membranes were cut out of the blood purifier, and then were subjected to an ~~eluation~~ elution test. As a result, the amount of eluting PVP was 5 ppm, and the maximum of the amount of eluting hydrogen peroxide was 2 ppm, both of which were levels of no problem. Further, the storage stability of the hollow fiber membrane bundle obtained in this Example was sufficient, since the maximum of the UV absorbance (220 to 350 nm) of the hollow fiber membrane bundle found after the storage thereof for one year was 0.06,

which was below 0.10 as a reference value, according to the Approval Standard for Dialysis-type Artificial Kidney Apparatus.

Please replace the paragraph beginning at page 67, line 1 with the following amended paragraph:

**[0090]** A blood purifier was fabricated, using the obtained hollow fiber membrane bundle, so as to carry out a leak test. As a result, there was observed no failure in adhesion due to the sticking of the hollow fiber membranes to one another. The blood purifier was filled with RO water, and then was irradiated with  $\gamma$ -ray at an absorbed dose of 25 kGy for a crosslinking treatment. After the irradiation with  $\gamma$ -ray, the hollow fiber membrane bundle was cut out of the blood purifier, and then was subjected to an ~~eluation~~ elution test. As a result, the amount of eluting PVP was 6 ppm, and the maximum of the amounts of eluting hydrogen peroxide was 2 ppm, both of which were levels of no problem. Further, the storage stability of the hollow fiber membrane bundle obtained in this Example was sufficient, since the maximum of the UV absorbance (220 to 350 nm) of the hollow fiber membrane bundle found after the storage thereof for one year was 0.06, which was maintained below 0.10 as a reference value according to the Approval Standard for Dialysis-type Artificial Kidney Apparatus. The hollow fiber membrane bundle was removed from the blood purifier, and the outer surface thereof was observed with a microscope. As a result, no defect such as flaws or the like was observed. In the blood leak test using bovine, no leakage of red blood cells was observed. The results of the analyses are shown in Table 3.

Please replace the paragraph beginning at page 69, line 11 with the following amended paragraph:

**[0092]** A blood purifier was fabricated, using the obtained hollow fiber membrane bundle. This blood purifier was not subjected to a crosslinking treatment by irradiation with  $\gamma$ -ray which was done in Example 2. The hollow fiber membrane bundle was cut out from the blood purifier and subjected to an ~~eluation~~ elution test. As result, the eluting amount of PVP was 12 ppm, and the maximal eluting amount of hydrogen peroxide was 20 ppm. The hydrogen peroxide elution of the hollow fiber membrane bundle of this Comparative Example was large, and therefore, the

storage stability thereof was inferior. This hollow fiber membrane bundle could not maintain the maximum UV absorbance (220 to 350 nm) below 0.10 as a reference value according to the Approval Standard for Dialysis-type Artificial Kidney Apparatus, after the storage thereof for about 3 months. Each of the blood purifiers was charged with a compressed air under a pressure of 0.1 MPa, and some blood purifiers, each showing a pressure decrease of 30 mmAq or less in 10 seconds, were used as modules to be tested. In blood leak tests using bovine blood, two out of 30 modules showed the leakage of red blood cells. This seemed to be attributed the occurrence of pin holes and/or tears of the hollow fiber membranes because of the small deviation in thickness and too large diameters of the pores of the outer surface of the hollow fiber membranes. The results are shown in Tables 1, 2 and 3.

Please replace the paragraph beginning at page 71, line 19 with the following amended paragraph:

**[0094]** A blood purifier was fabricated, using the obtained hollow fiber membrane bundle. The blood purifier was subjected to a leak test, with the result that no failure in adhesion attributed to the sticking of the hollow fiber membranes was observed. The blood purifier was filled with RO water, and then, the hollow fiber membrane bundle was cut out of the blood purifier and was subjected to an ~~eluation~~ elution test. As a result, the PVP elution was 7 ppm, and the maximum hydrogen peroxide elution was 3 ppm, which were levels of no problem. Each of the obtained blood purifiers was charged with a compressed air under a pressure of 0.1 MPa, and some of the blood purifiers which showed pressure drops of not higher than 30 mmAq for 10 seconds were used for the subsequent tests. The hollow fiber membrane bundle was removed from the blood purifier, and the outer surface thereof was observed with a microscope. As a result, no defect such as a flaw or the like was observed. Further, fresh bovine blood admixed with citric acid was allowed to pass through the blood purifier at a flow rate of 200 mL/minute and at a filtering rate of 10 mL/minute, with the result of no leakage of red blood cells. The amount of endotoxin filtered from the outside of the hollow fiber membranes to the inner side thereof was below the limit for detection, having a level of no problem. The storage stability of the hollow fiber membrane bundle obtained in this Example was sufficient, and the maximum of the UV absorbance (220 to 350 nm) of the follow fiber membrane bundle found after the storage thereof

for one year was 0.06, and was found to be kept below a reference value of 0.1 according to the Approval Standard for Dialysis-type Artificial Kidney Apparatus. As a result of the leak test, no failure in adhesion attributed to the sticking of the hollow fiber membranes was observed. The results are shown in Table 3.

Please replace the paragraph beginning at page 74, line 31 with the following amended paragraph:

**[0097]** A blood purifier was fabricated, using the obtained hollow fiber membranes. The blood purifier was subjected to a leak test, with the result that no failure in adhesion attributed to the sticking of the hollow fiber membranes was observed. The blood purifier was filled with RO water and subjected to a crosslinking treatment by irradiation with  $\gamma$ -ray at an absorbed dose of 25 kGy. After the irradiation with  $\gamma$ -ray, the hollow fiber membrane bundle was cut out of the blood purifier and subjected to an ~~elution~~ elution test. As a result, the PVP elution was 7 ppm, and the maximum hydrogen peroxide elution was 2 ppm, which were levels of no problem. Each of the blood purifiers as obtained above was charged with a compressed air under a pressure of 0.1 MPa, and some of the blood purifiers which showed pressure drops of not higher than 30 mmAq for 10 seconds were used for the subsequent tests. The hollow fiber membrane bundle was removed from the blood purifier, and the outer surface thereof was observed with a microscope. As a result, no defect such as a flaw or the like was observed. Further, fresh bovine blood admixed with citric acid was allowed to pass through the blood purifier at a flow rate of 200 mL/minute and at a filtering rate of 10 mL/minute, with the result of no leakage of red blood cells. The amount of endotoxin filtered from the outside of the hollow fiber membranes to the inner side thereof was below the limit for detection, having a level of no problem. The storage stability of the hollow fiber membrane bundle obtained in this Example was sufficient, and the maximum of the UV absorbance (220 to 350 nm) of the hollow fiber membrane bundle found after the storage thereof for one year was 0.07, and was found to be kept below a reference value of 0.1 according to the Approval Standard for Dialysis-type Artificial Kidney Apparatus. The results are shown in Table 3.